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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,096	07/26/2000	Robert M Umek	067456-5030-US	8157

67374 7590 08/23/2010

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
08/23/2010	PAPER

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ROBERT M. UMEK, GARY BLACKBURN,
BRUCE D. IRVINE, ROBERT H. TERBRUEGGEN,
CHANGJUN YU, and JOST G. VIELMETTER

Appeal 2010-002918
Application 09/626,096
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a method of identifying nucleotides in a target sequence. The Examiner has rejected

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

The Specification discloses methods "to electronically detect nucleic acids, particularly alterations such as nucleotide substitutions (mismatches) and single nucleotide polymorphisms (SNPs)" (Spec. 1: 8-10).

Claims 60-69 are on appeal. Claim 60 is the only independent claim and reads as follows:

> 60. A method of determining the identification of nucleotide(s) at a first detection position in a first domain of a target sequence, said target sequence comprising said first domain and a second domain, said method comprising:
>
> a. providing an electrode with a covalently attached capture probe, wherein said capture probe has a sequence substantially complementary to said second domain of said target sequence;
>
> b. contacting said electrode with:
>
> (i) said target sequence;
>
> (ii) a first label probe substantially complementary to said first domain, comprising a first nucleotide at an interrogation position and a first electron transfer moiety (ETM) with a first redox potential;
>
> (iii) a second label probe substantially complementary to said first domain, comprising a second nucleotide at said interrogation position and a second ETM with a second redox potential;
>
> under conditions wherein if said nucleotide at said interrogation position is perfectly complementary to said detection position, hybridization of said probe(s) occurs; and
>
> c. detecting the presence of said first and/or second ETM to determine the nucleotide(s) at said detection position.

Issue

The Examiner has rejected claims 60-69 under 35 U.S.C. § 103(a) as being obvious in view of Kayyem[2] and Shuber.[3]

The Examiner finds that Kayyem discloses the invention of claim 60 except for "using multiple ETM labeled probes for detecting the same domain" (Ans. 3-4). The Examiner finds that Shuber discloses "multiple oligonucleotide probes with labels for determining nucleotides at the detection position" (*id.* at 4) and concludes that it would have been obvious "to use the ETM labeled oligonucleotides, as taught by Kayyem et al. with the multiple oligonucleotide probes for mutation detection, as taught by Shuber" (*id.* at 5). The Examiner reasons that an "ordinary practitioner would have been motivated to use ETM labeled oligonucleotides … with the multiple oligonucleotide probes for mutation detection because Kayyem states that no electron transfer occurs unless nucleotide base pairing exists in the double stranded sequence between the electron donor and acceptor" (*id.*).

Appellants contend that the references do not suggest "contacting an electrode with … a second label probe comprising a second ETM with a second redox potential," as required by the claims (Appeal Br. 14).

The issue presented is: Does the evidence of record support the Examiner's conclusion that Kayyem and Shuber would have suggested contacting an electrode with two probes comprising different ETMs?

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[2] Kayyem et al., WO 98/20162, May 14, 1998
[3] Shuber, U.S. Patent 5,633,134, May 27, 1997

Findings of Fact

1. Kayyem discloses "nucleic acids covalently coupled to electrodes via conductive oligomers.... [T]he invention is directed to the site-selective modification of nucleic acids with electron transfer moieties and electrodes to produce a new class of biomaterials." (Kayyem, abstract.)

2. Kayyem discloses

> compositions comprising electrodes with conductive oligomers attached to probe nucleic acids, without second electron transfer moieties, and soluble second probe sequences with second electron transfer moieties. Upon binding of the target sequence, which contains a first target domain for the first probe sequence and a second target domain for the second probe sequence, which preferably are adjacent, electron transfer may occur.

(*Id.* at 36: 10-14.)

3. Shuber discloses "a process for analyzing a DNA sample for the presence of multiple mutations simultaneously using allele specific oligonucleotide probes (ASOs)" (Shuber, col. 1, ll. 54-57).

4. Shuber discloses that "[t]raditionally, ASOs have been radioactively end-labelled (e.g using ^{32}P or ^{35}S). However, ASOs can also be labelled by non-isotopic methods (e.g. via direct or indirect attachment of fluorochromes or enzymes, or by various chemical modifications of the nucleic acid fragments that render them detectable ...)." (*Id.* at col. 3, ll. 6-12.)

5. Shuber discloses that "hybridization can be detected using a means which is appropriate for the particular label used. For example, if ASOs are labelled radioactively, hybridization can be detected using autoradiography." (*Id.* at col. 4, ll. 8-11.)

Analysis

Claim 60 is directed to a method of determining the identification of a nucleotide at a detection position in a target sequence, and requires using two probes that each comprise a nucleotide at the position of interest and an electron transfer moiety (ETM). The claim does not expressly state that the probes differ in the nucleotide at the interrogation position and the attached ETM, but those limitations are implicit in the claim language: if the two probes were identical in sequence, they would not be "first" and "second" probes, and if each of the probes was attached to the same ETM, binding of the two probes could not be distinguished and therefore the method would not allow "identification of nucleotide(s) at a first detection position," as stated in the preamble.

Appellants argue that the cited references do not disclose "contacting an electrode with at least a second label probe comprising a second ETM with a second redox potential, and thus do not teach each and every limitation of the claims" (Appeal Br. 14). Appellants further argue that although Shuber discloses a method that uses multiple probes, "the multiple ASO probes in Shuber *all have the same label*" (*id.* at 13).

The Examiner responded to Appellant's argument by stating that "Shuber is not relied on to teach a second label probe comprising a second ETM" (Ans. 6) and that a "skilled artisan having read the disclosure of Kayeem [sic] et al. would recognize that ETMs as labels are distinguishable one from another and having read Shuber would also recognize the advantage of using such labels on probes when probing a single domain" (*id.*).

We agree with Appellants that the Examiner has not adequately explained how the references would have suggested modifying Kayyem's method to include multiple probes comprising different ETMs. The Examiner has not pointed to any disclosure in Kayyem or Shuber that shows the use of two differently labeled probes, for separate detection, in the same hybridization assay. Although the Examiner concludes that this limitation would have been obvious based on Kayyem, she has not pointed out any part of Kayyem that would have suggested to one of skill in the art using different ETMs having detectably different redox potentials in Kayyem's method.

It is the Examiner's burden to provide evidence that the claimed invention would have been obvious. In this situation, without any evidence on record that teaches or suggests differently labeled probes in a single assay, much less differentially detectable ETMs, we are constrained to reverse the obviousness rejection.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that Kayyem and Shuber would have suggested contacting an electrode with a two probes comprising different ETMs.

SUMMARY

We reverse the rejection of claims 60-69 under 35 U.S.C. § 103(a).

REVERSED

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